# FOOD AND DRUG ADMINISTRATION
# Center for Drug Evaluation and Research

## Background Materials

Meeting of the
Anesthetic and Analgesic Drug Products Advisory Committee
(AADPAC)

FDA White Oak Campus
Building 31, The Great Room (Rm. 1503)
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**December 7, 2012**

## DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 202880 to this Advisory Committee in order to gain the Committee's insights and opinions concerning the proposed drug product, Zohydro ER (hydrocodone bitartrate) Extended-Release Capsules, by Zogenix, Inc., for the proposed indication of management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

# TABLE OF CONTENTS

# 1 Division Director Memo

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

---

**M E M O R A N D U M**

---

DATE: November 8, 2012

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: Overview of the December 7, 2012 AADPAC Meeting to Discuss NDA 202880

---

At this meeting of the AADPAC we will be discussing Zogenix's NDA 202880 for Zohydro ER, hydrocodone bitartrate extended-release capsules, for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. If approved, Zohydro ER will be the first FDA approved, single-entity hydrocodone analgesic product.

The Applicant has provided the results of one adequate and well-controlled clinical trial of Zohydro ER conducted in patients with chronic low back pain. The safety of Zohydro ER was evaluated in over 1000 exposed subjects. The Applicant will present both the efficacy findings from the Phase 3 study, and the overall safety profile of Zohydro ER. Our colleagues from CDER's Office of Surveillance and Epidemiology will present usage data for hydrocodone combination products to provide some context for the potential extent of use of this single-entity hydrocodone product. They will also present epidemiological data on the abuse of

hydrocodone combination products compared to other combination opioid drug products that we hope will be helpful in providing some perspective on the potential abuse risk of Zohydro ER. In addition, there will be a presentation on the abuse liability studies of single-entity hydrocodone that have been performed by academic investigators.

Zohydro ER is an extended-release Schedule II opioid analgesic that falls within the class of drugs that are part of the Extended-Release/Long-Acting (ER/LA) Opioid Risk Evaluation and Mitigation Strategy (REMS). The proposed indication is the same as that for other extended-release opioid analgesics. We will be asking for your opinion as to whether the Applicant has provided adequate support for the safety and efficacy of Zohydro ER, whether the risk-benefit balance is in favor of approval, and whether the existing risk management tools, i.e., Schedule II under the Controlled Substances Act and the ER/LA REMS, are sufficient to address this opioid analgesic product's abuse liability in the post-marketing setting.

The Committee will be asked to consider the following on December 7, 2012:

1. **Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?**

2. **Has the applicant demonstrated that Zohydro ER is safe in the intended population?**

3. **Do any of the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids?**

4. **Are there data that support the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS?**

5. **Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?**

We are hopeful that your discussions and deliberations at this meeting of the AADPAC will assist us in determining whether or not the Sponsor has demonstrated substantial evidence of efficacy and an acceptable risk-benefit balance for Zohydro ER for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

# 2 Summary of Efficacy and Safety of Zohydro ER

Hydrocodone is a semisynthetic opioid analgesic and antitussive agent. Hydrocodone is currently marketed as a combination product containing hydrocodone and a non-opioid analgesic (e.g., acetaminophen or ibuprofen). Zohydro ER (hydrocodone bitartrate) extended-release capsules are being developed for the treatment of chronic pain as the first single-ingredient, extended-release hydrocodone product. On April 30, 2012, the Applicant, Zogenix Inc, submitted an NDA to the Agency, received May 1, 2012, seeking approval to market Zohydro ER for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time in adults.

Zohydro ER utilizes a proprietary multiparticulate oral drug delivery system (SODAS, Alkermes) composed of a mixture of immediate release and sustained release beads of hydrocodone. Zohydro ER strengths 10, 15, 20, 30, 40 and 50 mg have been submitted to the Agency for approval.

Hydrocodone drug substance is listed in Schedule II of the Controlled Substances Act (CSA). Hydrocodone combination products, containing a specified amount of hydrocodone and formulated with specified amounts of an isoquinoline alkaloid of opium, or one or more therapeutically active non-narcotic ingredients, are in Schedule III of the CSA, unless exempted or listed in another schedule. These combination products include marketed and approved analgesic and cough suppressant products. Although not currently available on the market, any product containing single entity hydrocodone, or combinations of hydrocodone and other substances outside the range of specified doses would be listed in Schedule II. Specifically, Schedule III controls apply to hydrocodone combination products containing no more than 300 milligrams per 100 milliliters or not more than 15 milligrams of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. Zohydro ER as a single entity hydrocodone product would be regulated under Schedule II.

The Applicant submitted one principal study (ZX002-0801) to support the efficacy of Zohydro ER for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Study ZX002-0801 was a randomized, placebo-controlled study with an open-label conversion/titration (C/T) phase of Zohydro ER followed by a randomized double-blind 12-week treatment phase of Zohydro ER vs. placebo in subjects with moderate-to-severe chronic low back pain (CLBP).

Eligibility criteria included a baseline pain score of at least 4 out of 10, pain present for at least several hours a day for a minimum of 3 months, and subjects receiving opioid therapy for at least 5 days/week for the 4 weeks prior to study entry at the

equivalent of at least an average daily dose of hydrocodone 30 mg (45 mg oral morphine equivalents) for treatment of CLBP.

The protocol-specified primary efficacy endpoint was the mean change from baseline to end of treatment (Day 85) in the average 24-hour pain intensity ratings as measured by an 11-point Numerical Rating Scale (NRS). Baseline was defined as the average of the last 7 days on stabilized dosing prior to randomization and end of treatment was defined as the average of the last 7 days prior to the Day 85 study visit. . An analysis of covariance model was used to evaluate the primary efficacy endpoint. Analyses were conducted on the intent-to-treat population including all randomized subjects receiving at least one dose of double-blind study drug.

Study ZX002-0801 demonstrated superiority of Zohydro ER over placebo. The mean change in pain intensity score from baseline to Day 85 was 0.48 ± 1.56 in the Zohydro ER group, and 0.96 ± 1.55 in the placebo group, and the difference was statistically significant (p=0.008). Efficacy was also supported by results of the analyses of the secondary endpoints including subjective global assessment of medication, worst pain intensity, and least pain intensity. A graphical depiction of the cumulative proportion of responders provided additional evidence of the efficacy of Zohydro ER.

In the Zohydro ER development program a total of 1512 subjects were exposed to at least one dose of Zohydro ER with 332 subjects exposed for 6 months or more and 290 subjects exposed for one year or more. The most frequently reported treatment-emergent adverse events (TEAEs) were consistent with the known opioid adverse event profile and included constipation, nausea, somnolence, fatigue, headache and dizziness.

Death occurred in five subjects in the development program. Four of the deaths did not appear directly related to Zohydro ER: completed suicide (carbon monoxide poisoning), drug toxicity (methadone and oxycodone), non-small cell lung cancer, and coronary artery arteriosclerosis. One drug death due to overdose was related to misuse of Zohydro ER. This death occurred after completion of the study in a subject who hoarded Zohydro ER capsules and then opened and ingested all the medication.

Serious adverse events that appeared possibly related to Zohydro ER based on the known opioid adverse event profile included nervous system disorders (i.e., mental impairment) and gastrointestinal disorders (i.e., constipation, small bowel obstruction and abdominal distension).

# 3 Drug Utilization Review

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

---

**M E M O R A N D U M**

---

DATE: November 9, 2012

FROM: The Division of Anesthesia, Analgesia and Addiction Products

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee

RE: Drug Utilization Review

---

The following drug utilization review was prepared by the Office of Surveillance and Epidemiology for inclusion in the background documents for the Drug Safety and Risk Management Advisory Committee (DSaRM) meeting that was scheduled for October 29 and 30, 2012 (postponed to a date yet to be determined), to examine drug utilization patterns for combination hydrocodone-containing products as compared to selected other opioid analgesics from the years 2007 through 2011. Although the purposes of the DSaRM meeting and the December 7, 2012 AADPAC meeting are different, this review is included here because it contains information on current use of other opiate products that we believe is relevant to discussions regarding the Zohydro ER NDA.

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

# Drug Utilization Review

| | |
|---|---|
| Date: | September 24, 2012 |
| Reviewer(s): | Rajdeep Gill, Pharm.D.<br>Drug Utilization Data Analyst<br>Division of Epidemiology II |
| Team Leader: | Hina Mehta, Pharm.D.<br>Drug Utilization Data Analysis Team Leader<br>Division of Epidemiology II |
| Director: | Judy Staffa, Ph.D., RPh,.<br>Division of Epidemiology II |
| Subject: | Drug Utilization for Hydrocodone-Containing Combination Products and Comparators |
| Drug Name(s): | Combination Hydrocodone-Containing Products and Comparators: oxycodone, morphine, hydromorphone |
| Application Type/Number: | Multiple |
| Applicant/sponsor: | Multiple |
| OSE RCM #: | 2012-1613 |

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**

# Table of Contents

## EXECUTIVE SUMMARY

In preparation for the Drug Safety and Risk Management Advisory Committee scheduled on October 29 and 30, 2012, this review examines drug utilization patterns for combination hydrocodone-containing products as compared to selected other opioid analgesics from year 2007 through 2011. Because the majority of hydrocodone-containing combination products were sold to U.S. outpatient retail pharmacies, this review focused on the outpatient retail pharmacy drug utilization patterns.

***Summary of Findings:***

- In year 2011, approximately 96% (131 million prescriptions) of combination hydrocodone-containing prescriptions dispensed through U.S. outpatient retail pharmacies were for the analgesic products and approximately 4% (5.3 million prescriptions) were for antitussive products.
- During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions.
- The greatest proportion of combination hydrocodone-containing prescriptions dispensed was prescribed by General Practice/Family Medicine/Osteopathic specialists followed by Internal Medicine.
- The average days of therapy for both combination hydrocodone-containing and combination oxycodone-containing prescriptions was approximately 14 days per prescription as compared to 27 days for single-ingredient extended-release oxycodone and 28 days for extended-release morphine prescriptions.
- According to a crude duration of use analysis, 50% of patients with combination hydrocodone-containing and combination oxycodone-containing prescription claims had therapy duration of 8 days and 6 days, respectively.
- According to U.S. office-based physician practices, the most common diagnoses codes associated with combination hydrocodone-containing products were for “Diseases of the Musculoskeletal System and Connective Tissue” (ICD-9 codes 710-739) followed by “Diseases of Respiratory System” (ICD-9 codes 462-493), and “Fractures, Sprains, Contusions and Injuries” (ICD-9 codes 800-999).

## 1 INTRODUCTION

The Controlled Substances Staff (CSS) is reviewing a request from the Drug Enforcement Agency (DEA) to reschedule hydrocodone combination products from Schedule III to Schedule II. In support of this assessment, the Division of Epidemiology was requested to provide the outpatient retail drug utilization patterns for combination hydrocodone-containing products and selected comparator drug products: combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone from year 2007 through year 2011, annually.

# 2 BACKGROUND

## 2.1 PRODUCT LABELLING

Hydrocodone is an opioid agonist indicated for symptomatic relief of moderate to moderately severe pain in combination with acetaminophen or NSAIDS; as well as, symptomatic relief of nonproductive cough in combination with antitussives or expectorants.[1,2] Under the Controlled Substance Act (CSA), the Drug Enforcement Administration (DEA), classifies single ingredient hydrocodone as Schedule II controlled substance (not currently marketed) and combination hydrocodone products containing less than 15mg of hydrocodone per dosage unit (such as hydrocodone/acetaminophen, hydrocodone/chlorpheniramine) as Schedule III controlled substances.[3] The Controlled Substances Staff (CSS) received a request from the DEA for a scientific and medical evaluation and scheduling recommendation to re-classify hydrocodone-containing products to Schedule II controlled substances. On October 29 and 30, 2012 the Drug Safety and Risk Management Advisory Committee will be convened to discuss the public health benefits and risks of reclassifying hydrocodone-containing products to Schedule II controlled substances.

## 2.2 PRODUCTS INCLUDED[4]

Hydrocodone-containing combination products (analgesics) utilization is compared to the following various single ingredient and combination opioid analgesics.
*Of note, all the comparator drugs are Schedule II controlled substances.*

| Drug | |
|---|---|
| Combination hydrocodone-containing products | Hydrocodone/Acetaminophen<br><br>Hydrocodone/Ibuprofen<br><br>Hydrocodone/Aspirin |
| Combination oxycodone-containing products | Oxycodone/Acetaminophen<br><br>Oxycodone/Ibuprofen<br><br>Oxycodone/Aspirin |
| Single-ingredient oxycodone products | Immediate-release oxycodone<br><br>Extended-release oxycodone |
| Morphine sulfate | Immediate-release morphine sulfate<br><br>Extended-release morphine sulfate |
| Hydromorphone | Immediate-release hydromorphone |

1 http://www.drugs.com/monograph/hydrocodone-bitartrate.html
2 http://www.deadiversion.usdoj.gov/drugs_concern/hydrocodone.pdf
3 http://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf
4 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

| | |
|---|---|
| | Extended-release hydromorphone |

# 3 METHODS AND MATERIALS

## 3.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives™ database (see ***Appendix 2*** for full database description) was used to determine the various retail and non-retail channels of distribution for hydrocodone. Sales data for year 2011 indicated that approximately 95% of hydrocodone-containing products were sold as combination hydrocodone/acetaminophen of which, approximately 65% of combination hydrocodone/acetaminophen bottles (Eaches) were distributed to outpatient retail pharmacies, 28% to non-retail settings; and 7% to mail order pharmacies. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies.[5] As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail-order/specialty pharmacies nor non-retail settings data were included in this analysis.

## 3.2 DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis. (See ***Appendix 2***).

The IMS Health, IMS National Sales Perspective™ database was used to obtain the estimated weight in kilograms of selected opioids, which include combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone sold from manufacturers to various channels of distribution for years 2007 through 2011. Additionally, the sales distribution of combination hydrocodone-containing antitussive products was examined in terms of extended units (number of tablets, capsules, milliliters, etc.). These sales data represent the amount of product being sold from manufacturers into the "back door" of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly.

U.S. outpatient retail pharmacy drug utilization for combination hydrocodone/acetaminophen, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone was obtained from the IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT) databases. From these two sources, nationally projected estimates of the number of prescriptions dispensed and unique patients who received a dispensed prescription were obtained for years 2007 through year 2011, annually. Additionally, the average days of therapy dispensed to patients for a product (therapy days divided by prescriptions) and top specialties prescribing selected opioids were also obtaining from IMS Health, Vector One®: National (VONA).

5 IMS Health, National Sales Perspectives™. Extracted Sept 2012. File: NSPC 2012-1613 Hydrocodone combo sales 09-17-12.xlsx

Diagnoses associated with the use of combination hydrocodone/acetaminophen and comparator drugs were obtained from the Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) for years 2007-2011, cumulative.

## 3.3 DURATION OF THERAPY METHODOLOGY

The Source Healthcare Analytics' ProMetis Lx® Concurrent Product Analyzer (CPA) was used to examine the therapy duration episode for combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, and single-ingredient extended-release oxycodone in deciles to determine the length of therapy for patients using these products for year 2010 through 2011, cumulative. An episode is defined as the period of time that a patient has uninterrupted therapy with a product or group of products (regimen). The duration of an episode is the number of days between the start and end dates of the episode, which is determined by summing days' supply of all prescriptions. The total episode duration is the sum of the days for each episode for a product within the selected study period. Product deciles are based on a frequency distribution of the therapy durations for each patient having the specified product. Based on the minimum and the maximum therapy duration, patients are divided into 10 equal groups or deciles.

# 4 RESULTS

### 4.1 SALES DISTRIBUTION OF COMBINATION HYDROCODONE-CONTAINING PRODUCTS (ANALGESICS) AND COMPARATOR DRUGS

***Figure 1 in Appendix 1*** shows the weight in kilograms of combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient extended-release oxycodone, single-ingredient immediate-release oxycodone, extended-release morphine, immediate-release morphine, and hydromorphone; sold from manufacturers to various channels of distribution for years 2007 through 2011. Throughout the time examined, the weight in kilograms sold of combination hydrocodone-containing products has been the market lead when compared to the selected opioids analyzed. Approximately 64,000 kilograms of combination hydrocodone-containing products were sold during year 2011 accounting for a 28% increase from 50,000 kilograms sold during year 2007. There was more than a 3-fold increase in the weight in kilograms sold of immediate-release oxycodone from 10,000 kilograms sold during year 2007 to about 33,000 kilograms sold during year 2011. The weight in kilograms sold of extended-release oxycodone stayed relatively steady until year 2010 after which there was a 25% decrease to about 19,000 kilograms sold. The other agents analyzed such as combination oxycodone-containing products, extended-release morphine, immediate-release morphine, and hydromorphone have gradually increased in the amount of kilograms sold during the time period examined.

### 4.2 SALES DISTRIBUTION OF HYDROCODONE-CONTAINING ANTITUSSIVES

***Figure 2 in Appendix 1*** shows the number of extended units (tablets/capsules/mls) of combination antitussive hydrocodone-containing products sold from the manufactures to various channels of distribution from year 2007 through 2011. The number of extended units sold for combination antitussive hydrocodone-containing products decreased by 59% from approximately

1.9 billion extended units sold during year 2007 to approximately 772 million extended units sold during year 2011.

### 4.3 Outpatient Dispensed Prescriptions for Hydrocodone Combination Products (analgesics and antitussives)

***Table 1 in Appendix 1*** shows the estimated number of prescriptions for combination hydrocodone-containing products, stratified as analgesics and antitussives, dispensed from U.S. outpatient pharmacies for years 2007 through 2011. Throughout the time period examined, analgesic combination hydrocodone-containing products accounted for the majority of prescriptions (91%-96% of total) dispensed.

During year 2011 approximately 131 million analgesic combination hydrocodone-containing prescriptions were dispensed through U.S. outpatient retail pharmacies. The number of antitussive combination hydrocodone-containing prescriptions dispensed decreased from approximately 12 million prescriptions (9% of total) during year 2007 to approximately 5.3 million prescriptions (4% of total) during year 2011.

### 4.4 Outpatient Dispensed Prescriptions for combination Hydrocodone-containing Products (analgesics) and comparators

***Table 2 in Appendix 1*** shows the estimated number of combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone dispensed from U.S. outpatient retail pharmacies for years 2007 through 2011. Throughout the time period examined, combination hydrocodone-containing products accounted for the majority of prescriptions (66%-70% of total) dispensed followed by oxycodone-containing products (25%-29% of total). During year 2011, approximately 131 million (66% of total) combination hydrocodone-containing prescriptions were dispensed followed by 57 million (29% of total) oxycodone-containing prescriptions of which, 34.6 million were of combination oxycodone-containing products and 22.3 million were of single-ingredient oxycodone. Of the single-ingredient oxycodone prescriptions dispensed approximately 16.6 million (74% of single-ingredient oxycodone) prescriptions dispensed were immediate-release oxycodone and about 5.7 million (26% of single-ingredient oxycodone) were extended-release oxycodone during year 2011. Approximately 7.6 million (4% of total) morphine prescriptions were dispensed and 2.7 million (1% of total) hydromorphone prescriptions were dispensed during year 2011. The number of prescriptions dispensed increased for all of the agents analyzed with the exception of extended-release oxycodone which decreased during the time examined.

### 4.5 Number of Patients Receiving Hydrocodone-Containing Products (analgesics) and Comparators Drugs

***Figure 3 in Appendix 1*** shows the estimated number of unique patients receiving combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone, single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone dispensed from outpatient retail

pharmacies for years 2007 through 2011. Throughout the time period examined, a greater number of patients received combination hydrocodone-containing prescriptions followed by patients receiving combination oxycodone-containing prescriptions. During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions. Approximately 4.1 million patients received dispensed immediate-release oxycodone prescriptions while 1.2 million patients received dispensed extended-release oxycodone prescriptions during year 2011. The number of patients receiving dispensed prescriptions increased for all of the agents analyzed with the exception of extended-release oxycodone in which the number of patients decreased during the time examined.

### 4.6 TOP PRESCRIBERS

***Table 3 in Appendix 2*** provides the number of outpatient retail dispensed prescriptions for combination hydrocodone-containing products, combination oxycodone-containing products, single-ingredient immediate-release oxycodone single-ingredient extended-release oxycodone, immediate-release morphine, extended-release morphine, and hydromorphone by top prescribing specialties. Over the cumulative time period from year 2007 to year 2011, General Practice/Family Medicine/Doctor of Osteopathy specialists were the top prescribing specialty accounting for approximately one-fifth to one-quarter of total prescriptions dispensed for each agent analyzed. Internal Medicine specialists followed accounting for approximately 13%-18% of total prescriptions dispensed for each agent analyzed. Dentists accounted for approximately 10% (65 million prescriptions) of the total combination hydrocodone-containing prescriptions dispensed and approximately 5% (8.6 million prescriptions) of the total combination oxycodone-containing prescriptions dispensed. The number of dispensed prescriptions prescribed by orthopedic surgeons was relatively higher for combination hydrocodone-containing products (8% or 52 million prescriptions) and combination oxycodone-containing products (9% or 14.2 million prescriptions) as compared to the other opioid analgesics analyzed: extended-release oxycodone (4% or 1.5 million prescriptions), immediate-release oxycodone (4% or 2.4 million prescriptions), extended-release morphine (1% or 313,000 prescriptions), immediate-release morphine (less than 1% or 49,000 prescriptions), and hydromorphone (5% or 547,000 prescriptions). In contrast, the number of prescriptions prescribed by anesthesiologists was relatively lower for combination hydrocodone-containing products (3% or 16.3 million prescriptions) and combination oxycodone-containing products (4% or 6.9 million prescriptions) as compared to other opioid analgesics analyzed: extended-release oxycodone (10% or 3.9 million prescriptions), immediate-release oxycodone (9% or 4.8 million prescriptions), extended-release morphine (15% or 3.9 million prescriptions), immediate-release morphine (12% or 863,000 prescriptions) and hydromorphone (5% or 547,000 prescriptions).

In general, we observed similar prescribing patterns for combination hydrocodone-containing products and combination oxycodone-containing products during the time period examined.

### 4.7 AVERAGE DAYS OF THERAPY PER PRESCRIPTION

***Figure 4 in Appendix 2*** shows the average days of therapy per prescription for combination hydrocodone-containing products as compared to various other opioid analgesics for year 2011. The average days of therapy for both combination hydrocodone-containing and combination oxycodone-containing prescriptions was approximately 14 days per prescription. Comparatively, the average days of therapy per prescription for extended-release formulations was higher with approximately 27 days for single-ingredient extended-release oxycodone and approximately 28 days for extended-release morphine. The average days of therapy per prescription for single-ingredient immediate-release oxycodone were approximately 22 days and approximately 18 days for immediate-release morphine. The average days of therapy per hydromorphone prescription was approximately 17 days.

### 4.8 DURATION OF USE ANALYSIS

***Table 4 in Appendix 2*** shows the median and mean duration of therapy in days for combination hydrocodone-containing , combination oxycodone-containing, single-ingredient, immediate-release oxycodone, and single-ingredient, extended-release oxycodone prescription claims in an unprojected patient sample for years 2010 through 2011, cumulative. The median episode duration for combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone were 8 days, 6 days, 19 days, and 31 days, respectively. The mean episode duration for combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone were 45 days, 30 days, 72 days, and 43 days, respectively.

In addition, we examined the minimum and maximum days of therapy for patients with combination hydrocodone-containing products, combination oxycodone-containing products, immediate-release oxycodone, and extended-release oxycodone therapy to determine the estimated proportion of patients with therapy duration for each agent. Based on the minimum and the maximum therapy duration, patients were divided into 10 equal groups or deciles. Approximately 70% of patients with combination hydrocodone-containing product prescriptions claims had therapy duration of 16 days or less. We estimate that approximately 20% of the patient sample used combination hydrocodone-containing products for 32 days or longer. Approximately 70% of patients with combination oxycodone-containing product prescription claims had therapy duration of 12 days or less. We estimate that approximately 20% of the patient sample used combination oxycodone-containing products for 23 days or longer. Approximately 70% of patients with immediate-release oxycodone prescription claims had therapy duration of 31 days or less. We estimate that approximately 20% of the patient sample used immediate-release oxycodone agents for 93 days or longer. Approximately 60% of patients with extended-release oxycodone prescription claims had therapy duration of 31 days or less. We estimate that approximately 10% of the patient sample used extended-release oxycodone agents for 100 days or longer.

### 4.9 INDICATIONS FOR USE

***Table 5 in Appendix 2*** shows the most common diagnoses associated with the use of combination hydrocodone-containing products as compared to combination oxycodone-containing products,

single-ingredient, extended-release oxycodone, single-ingredient, immediate-release oxycodone, extended-release morphine, immediate-release morphine, and hydromorphone. The number of drug use mentions[6] for hydromorphone and extended release oxycodone from office-based physician visits was below the acceptable count allowable to provide a reliable estimate of national use. Over the cumulative time period from year 2007 through 2011, "Diseases of the Musculoskeletal System and Connective Tissue" (ICD-9 codes 710-739) were the most common diagnoses associated with the use of all opioid analgesics analyzed; with approximately 25% of the total drug use mentions for combination hydrocodone-containing products, 20% of drug use mentions for combination oxycodone-containing products, 41% of drug use mentions for immediate-release oxycodone, 68% of drug use mentions for extended-release morphine, and 56% of drug use mentions for immediate-release morphine.

The second most common diagnoses associated with the use of combination hydrocodone-containing products was "Diseases of Respiratory System" (ICD-9 codes 462-493), with approximately 21% of the total drug use mentions followed by "Fractures, Sprains, Contusions and Injuries" (ICD-9 codes 800-999) with approximately 19% of the total drug use mentions. Similar patterns were observed for combination oxycodone-containing products in terms of diagnoses, with the only difference observed for conditions associated with "Diseases of Respiratory System" (ICD-9 codes 462-493), likely due to the antitussive indication of some combination hydrocodone-containing products.

## 5 DISCUSSION

Throughout the time examined, the weight in kilograms sold of combination hydrocodone-containing products has been the market lead when compared to the other selected opioids analyzed. During year 2011 approximately 131 million analgesic combination hydrocodone-containing prescriptions were dispensed as compared to 5.3 million antitussive combination hydrocodone-containing prescriptions dispensed through U.S. outpatient retail pharmacies. During year 2011, approximately 47.1 million patients received dispensed prescriptions for combination hydrocodone-containing prescriptions followed by 15.1 million patients receiving dispensed prescriptions for combination oxycodone-containing prescriptions. Prescribing patterns for combination hydrocodone-containing products and combination oxycodone-containing products were very similar.

The greatest proportion of drug use mentions for combination hydrocodone-containing products was associated with the use of "Diseases of the Musculoskeletal System and Connective Tissue" (ICD-9 codes 710-739) followed by "Diseases of Respiratory System" (ICD-9 codes 462-493), and "Fractures, Sprains, Contusions and Injuries" (ICD-9 codes 800-999). Similar patterns were observed for combination oxycodone-containing products in terms of diagnoses, with the only difference observed for conditions associated with "Diseases of Respiratory System" (ICD-9

6 Encuity Research, LLC., uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

codes 462-493), likely due to the antitussive indication of some combination hydrocodone-containing products.

Furthermore, our analysis of average days of therapy per dispensed prescription as well duration of therapy analysis showed that combination hydrocodone-containing products and combination oxycodone-containing products were used for shorter time period (about 14 days) as compared to extended-release oxycodone (about 27 days) and extended-release morphine prescriptions (about 28 days).

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that combination hydrocodone-containing products are distributed primarily to the outpatient setting. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

We focused our analysis on only the outpatient retail pharmacy setting, therefore these estimates may not apply to other settings of care in which these products are used (e.g. mail-order/specialty pharmacy, and non-retail pharmacies). The estimates provided are national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Data from Source Healthcare Analytics' ProMetis Lx® provides *unprojected* patient counts with a prescription claim for selected opioids. Due to the sample size and the unreported pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of mail order and specialty pharmacies contributing to these data are unknown. Duration of therapy counts are based on the sample data only; therefore, they are not projected to national estimates.

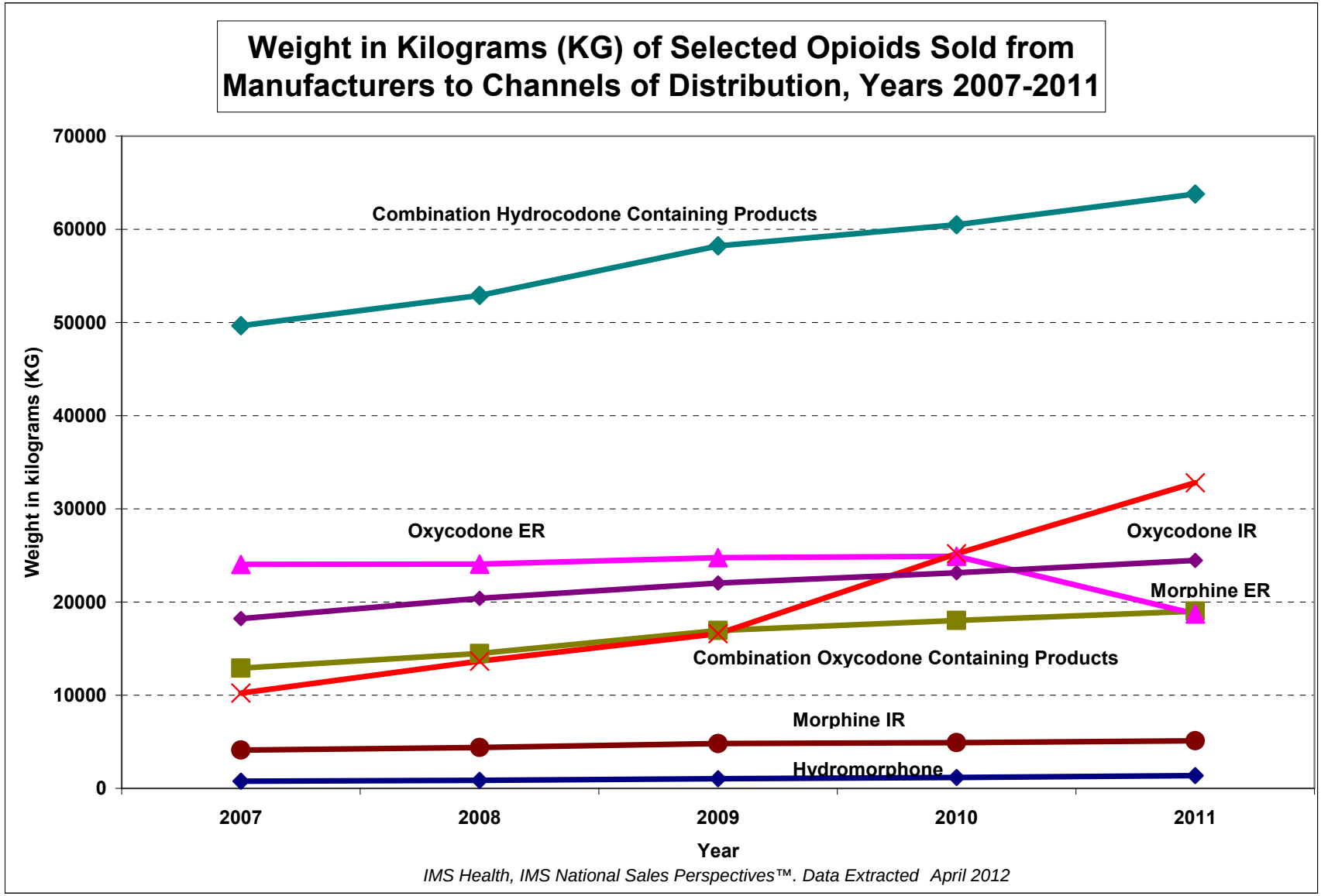
Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice. Encuity Research, LLC., recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

## 6 CONCLUSIONS

In year 2011, approximately 131 million prescriptions were dispensed and 47.1 million patients received a dispensed prescription for combination hydrocodone-containing analgesic products. Similar to combination oxycodone-containing products, combination hydrocodone-containing products had an average 14 days of therapy and were most commonly prescribed by General Practice/Family Medicine/Doctor of Osteopathy and Internal Medicine specialists and were used for conditions associated “Diseases of the Musculoskeletal System and Connective Tissue” (ICD-9 codes 710-739) followed by “Diseases of Respiratory System” (ICD-9 codes 462-493), and “Fractures, Sprains, Contusions and Injuries” (ICD-9 codes 800-999).

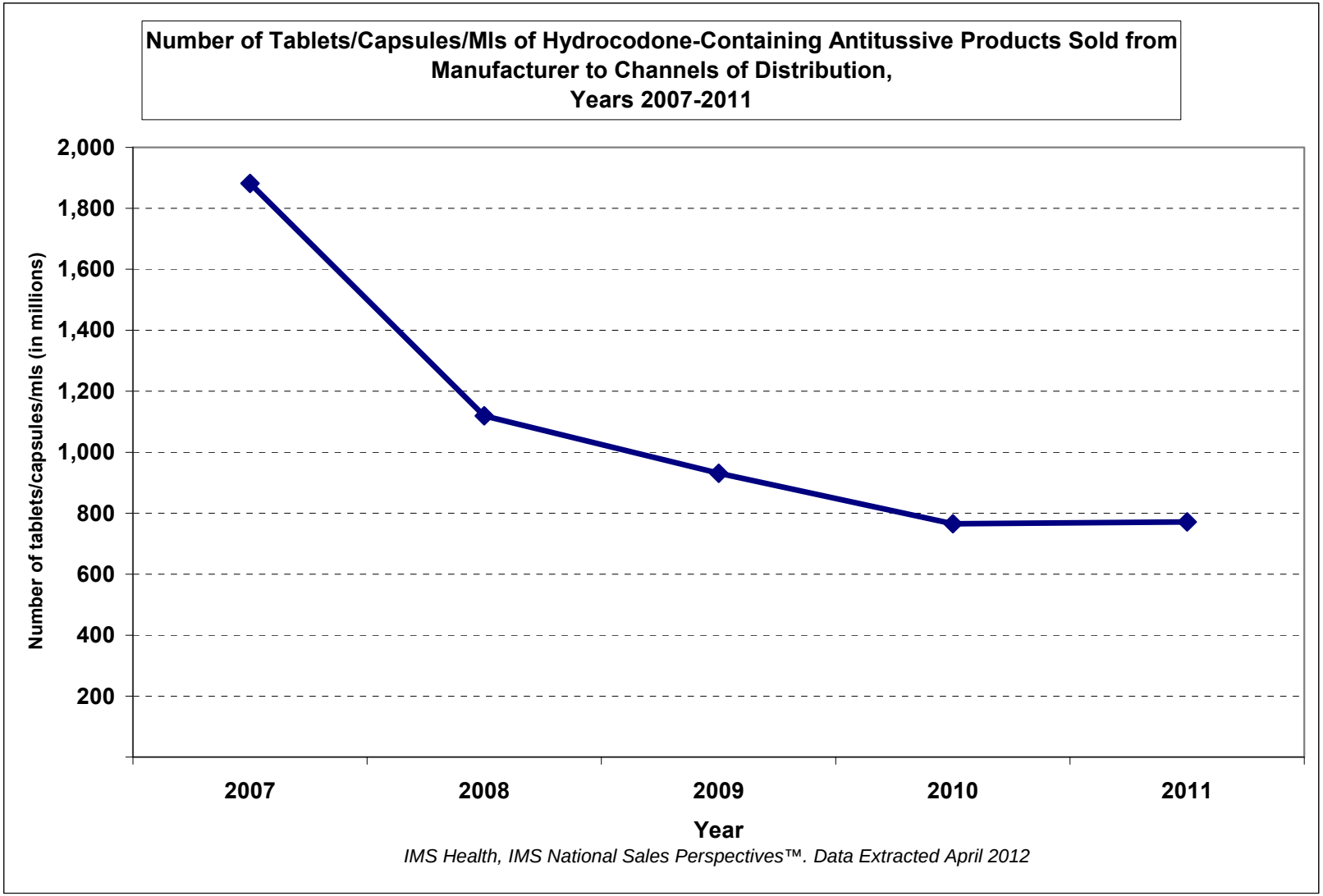
# APPENDIX 1: TABLES AND FIGURES

**FIGURE 1.**


Weight in Kilograms (KG) of Selected Opioids Sold from Manufacturers to Channels of Distribution, Years 2007-2011
Weight in kilograms (KG)
70000
60000
50000
40000
30000
20000
10000
0
2007
2008
2009
2010
2011
Year
Combination Hydrocodone Containing Products
Oxycodone ER
Oxycodone IR
Morphine ER
Combination Oxycodone Containing Products
Morphine IR
Hydromorphone
IMS Health, IMS National Sales Perspectives™. Data Extracted April 2012

1.

**FIGURE 2.**


Number of Tablets/Capsules/Mls of Hydrocodone-Containing Antitussive Products Sold from Manufacturer to Channels of Distribution, Years 2007-2011
Number of tablets/capsules/mls (in millions)
2,000
1,800
1,600
1,400
1,200
1,000
800
600
400
200
2007
2008
2009
2010
2011
Year
IMS Health, IMS National Sales Perspectives™. Data Extracted April 2012

## TABLE 1

**Nationally Estimated Number of Prescriptions for Combination Hydrocodone-Containing Products, Stratified as Analgesics and Antitussives, Dispensed from U.S. Outpatient Retail Pharmacies for years 2007 through 2011**

| | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TRxs N | *Share %* | TRxs N | *Share %* | TRxs N | *Share %* | TRxs N | *Share %* | TRxs N | *Share %* |
| **TOTAL MARKET** | 132,718,152 | *100.0%* | 133,322,635 | *100.0%* | 129,925,065 | *100.0%* | 130,855,251 | *100.0%* | 135,985,813 | *100.0%* |
| **Hydrocodone Analgesic Products** | **120,558,365** | ***90.8%*** | **124,638,176** | ***93.5%*** | **123,785,711** | ***95.3%*** | **125,749,238** | ***96.1%*** | **130,704,028** | ***96.1%*** |
| **Hydrocodone Antitussive Products** | 12,159,786 | *9.2%* | 8,684,459 | *6.5%* | 6,139,354 | *4.7%* | 5,106,013 | *3.9%* | 5,281,785 | *3.9%* |

*Source: IMS Health, Vector One®: National. Data Extracted 9-12-12. File: VONA 2009-2039 Hydrocodone Products Analgesics and Cough Cold 9-12-12.xls*

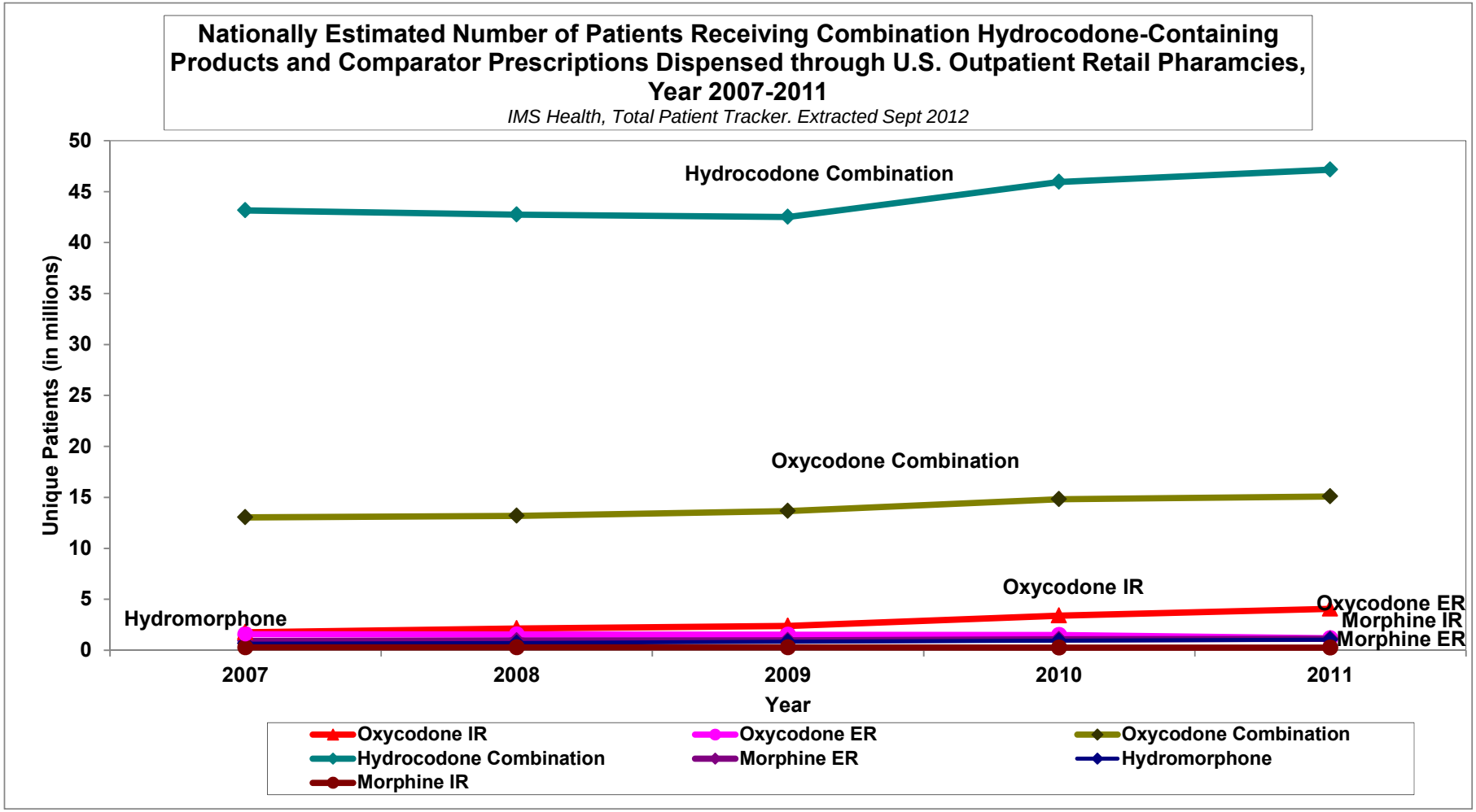
## TABLE 2

**Nationally Estimated Number of Combination Hydrocodone-Containing and Comparators (Oxycodone ER/IR, Combination oxycodone-containing, Morphine ER/IR, and Hydromorphone) Prescriptions Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011**

| | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* |
| **Total Market** | **171,193,887** | ***100.0%*** | **180,024,122** | ***100.0%*** | **181,834,902** | ***100.0%*** | **189,517,906** | ***100.0%*** | **198,092,751** | ***100.0%*** |
| **Hydrocodone Analgesic Products** | **120,558,352** | ***70.4%*** | **124,638,107** | ***69.2%*** | **123,785,684** | ***68.1%*** | **125,749,235** | ***66.4%*** | **130,704,029** | ***66.0%*** |
| ***Hydrocodone/Acetaminophen*** | 118,074,137 | 97.9% | 122,260,964 | 98.1% | 121,575,144 | 98.2% | 123,556,210 | 98.3% | 128,546,058 | 98.3% |
| ***Hydrocodone/Ibuprofen*** | 2,484,184 | 2.1% | 2,377,134 | 1.9% | 2,210,530 | 1.8% | 2,193,014 | 1.7% | 2,157,965 | 1.7% |
| ***Hydrocodone/Aspirin*** | 31 | 0.0% | 9 | 0.0% | 10 | 0.0% | 11 | 0.0% | 6 | 0.0% |
| **Total Oxycodone** | 43,405,133 | *25.4%* | 47,225,509 | *26.2%* | 49,419,388 | *27.2%* | 54,365,207 | *28.7%* | 56,983,248 | *28.8%* |
| **Oxycodone Combination** | 28,803,782 | *66.4%* | 30,805,888 | *65.2%* | 32,239,395 | *65.2%* | 33,704,239 | *62.0%* | 34,653,743 | *60.8%* |
| ***Oxycodone/Acetaminophen*** | 28,545,736 | *99.1%* | 30,596,686 | *99.3%* | 32,074,676 | *99.5%* | 33,569,445 | *99.6%* | 34,545,056 | *99.7%* |
| ***Oxycodone/Aspirin*** | 206,142 | *0.7%* | 179,246 | *0.6%* | 144,547 | *0.4%* | 120,401 | *0.4%* | 99,233 | *0.3%* |
| ***Oxycodone/Ibuprofen*** | 51,904 | *0.2%* | 29,956 | *0.1%* | 20,172 | *0.1%* | 14,393 | *0.0%* | 9,454 | *0.0%* |
| **Oxycodone Single Ingredient** | 14,601,351 | *33.6%* | 16,419,621 | *34.8%* | 17,179,993 | *34.8%* | 20,660,968 | *38.0%* | 22,329,505 | *39.2%* |
| ***Oxycodone Immediate Release*** | 6,304,442 | *43.2%* | 8,093,643 | *49.3%* | 9,134,757 | *53.1%* | 13,190,814 | *63.7%* | 16,591,561 | *74.3%* |
| ***Oxycodone Extended Release*** | 8,296,909 | *56.8%* | 8,325,977 | *50.7%* | 8,045,237 | *46.8%* | 7,470,153 | *36.2%* | 5,737,943 | *25.7%* |
| **Morphine Sulfate** | 5,581,911 | *3.3%* | 6,299,627 | *3.5%* | 6,463,446 | *3.6%* | 6,981,624 | *3.7%* | 7,635,623 | *3.9%* |
| ***Morphine ER*** | 4,236,471 | *75.9%* | 4,822,350 | *76.5%* | 5,104,791 | *79.0%* | 5,619,457 | *80.5%* | 6,053,915 | *79.3%* |
| ***Morphine IR*** | 1,345,440 | *24.1%* | 1,477,276 | *23.5%* | 1,358,655 | *21.0%* | 1,362,166 | *19.5%* | 1,581,708 | *20.7%* |
| **Hydromorphone** | 1,618,707 | *0.9%* | 1,833,332 | *1.0%* | 2,135,612 | *1.2%* | 2,387,752 | *1.3%* | 2,735,846 | *1.4%* |

*Source: IMS, Vector One®: National (VONA), extracted 09/ 2012, Source Files: VONA_2012-2002_Hydrocodone,_oxycodone,_morphine,_hydromorphone_09-20-12(1).xls; VONA_2012-1613_Oxycodone_forms_09-20-12(1).xls; VONA_2012-1613_Morphine_IR_and_ER_09-20-12(1).xls*

**FIGURE 3**


Nationally Estimated Number of Patients Receiving Combination Hydrocodone-Containing Products and Comparator Prescriptions Dispensed through U.S. Outpatient Retail Pharamcies, Year 2007-2011
IMS Health, Total Patient Tracker. Extracted Sept 2012
Unique Patients (in millions)
50
45
40
35
30
25
20
15
10
5
0
Hydrocodone Combination
Oxycodone Combination
Oxycodone IR
Oxycodone ER
Morphine IR
Morphine ER
Hydromorphone
2007
2008
2009
2010
2011
Year
Oxycodone IR
Oxycodone ER
Oxycodone Combination
Hydrocodone Combination
Morphine ER
Hydromorphone
Morphine IR

## TABLE 3

**Number of Prescriptions Dispensed for Selected Opioids by Top Prescribing Specialties Through U.S. Outpatient Retail Pharmacies, Years 2007-2011 cumulative**

| | Hydrocodone Combination | | Oxycodone Combination | | Oxycodone IR | | Oxycodone ER | | Morphine IR | | Morphine ER | | Hydromorphone | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* | TRx | *Share %* |
| **General Practice/Family Practice/Osteopathy** | 160,181,555 | *25.6%* | 29,961,318 | *18.7%* | 12,436,964 | *23.3%* | 10,133,854 | *26.8%* | 1,790,752 | *25.1%* | 6,374,048 | *24.7%* | 1,829,683 | *17.3%* |
| **Internal Medicine** | 87,793,125 | *14.0%* | 20,013,405 | *12.5%* | 7,911,481 | *14.8%* | 6,399,322 | *16.9%* | 1,268,562 | *17.8%* | 3,860,351 | *14.9%* | 1,552,896 | *14.7%* |
| **Orthopedic Surgery** | 51,929,989 | *8.3%* | 14,248,303 | *8.9%* | 2,352,884 | *4.4%* | 1,534,447 | *4.1%* | 49,483 | *0.7%* | 312,570 | *1.2%* | 546,514 | *5.2%* |
| **Unspecified** | 35,074,830 | *5.6%* | 9,389,016 | *5.9%* | 4,344,635 | *8.1%* | 2,332,718 | *6.2%* | 516,725 | *7.3%* | 1,864,053 | *7.2%* | 720,932 | *6.8%* |
| **Physician Assistant** | 24,076,466 | *3.8%* | 8,007,884 | *5.0%* | 2,617,768 | *4.9%* | 1,440,433 | *3.8%* | 225,019 | *3.2%* | 1,186,162 | *4.6%* | 527,334 | *5.0%* |
| **Nurse Practitioner** | 20,914,534 | *3.3%* | 5,748,315 | *3.6%* | 2,993,887 | *5.6%* | 1,875,406 | *5.0%* | 384,056 | *5.4%* | 1,736,995 | *6.7%* | 462,020 | *4.4%* |
| **Dentist** | 64,867,932 | *10.4%* | 8,568,981 | *5.3%* | 178,467 | *0.3%* | 50,349 | *0.1%* | 8,073 | *0.1%* | 23,529 | *0.1%* | 48,238 | *0.5%* |
| **Anesthesiologists** | 16,299,925 | *2.6%* | 6,863,668 | *4.3%* | 4,831,093 | *9.1%* | 3,888,158 | *10.3%* | 863,447 | *12.1%* | 3,944,589 | *15.3%* | 546,514 | *5.2%* |
| **All Others** | 164,297,047 | *26.4%* | 57,406,156 | *35.8%* | 15,647,914 | *29.3%* | 10,221,531 | *27.0%* | 2,019,129 | *28.3%* | 6,534,687 | *25.3%* | 4,360,474 | *41.2%* |

*Source: IMS, Vector One®: National (VONA) Extracted September 2012. Source File: VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA 2012-1613 Morphine IR and ER by Specialty 9-25-12.xls; VONA_2012-1613_hydromorphone_specialties_09-25-12(1).xls; VONA_2012-1613_Oxycodone_Combo_Specialties_09-25-12(1).xls; VONA_2012-1613_Hydrocodone_Specialties_09-25-12(1).xls*

**FIGURE 4.**

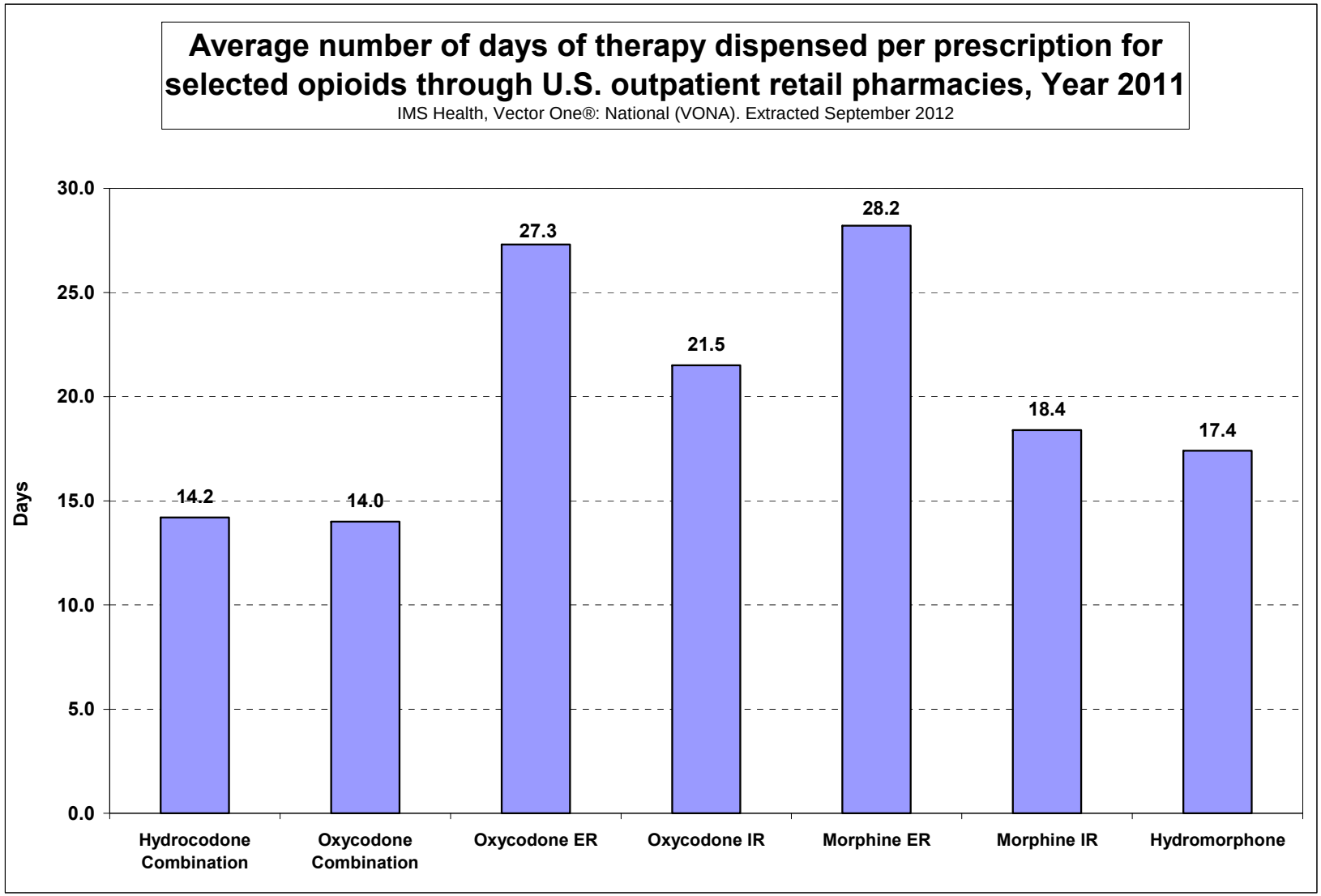

Average number of days of therapy dispensed per prescription for selected opioids through U.S. outpatient retail pharmacies, Year 2011
IMS Health, Vector One®: National (VONA). Extracted September 2012
Days
30.0
25.0
20.0
15.0
10.0
5.0
0.0
14.2
14.0
27.3
21.5
28.2
18.4
17.4
Hydrocodone Combination
Oxycodone Combination
Oxycodone ER
Oxycodone IR
Morphine ER
Morphine IR
Hydromorphone

**TABLE 4.**

**Crude days of therapy for selected opioids in a sample of patients**
**Cumulative January 2010 through December 2011**

| | | Days of Therapy | | | |
|---|---|---|---|---|---|
| Regimen | Number of sample patients | Median | Average | Min | Max |
| HYDROCODONE COMBO | 16,281,353 | 8 | 45.1 | 2 | 730 |
| OXYCODONE COMBO | 5,497,455 | 6 | 30.0 | 2 | 730 |
| OXYCODONE IR | 1,168,258 | 19 | 72.4 | 2 | 730 |
| OXYCODONE ER | 70,654 | 31 | 42.6 | 2 | 664 |

*Source: Source Healthcare Analytics ProMetis Lx®, January 2010-December 2011, extracted January, 2011,*
*Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12.xls*

**Estimated Duration of Therapy by Deciles for a Sample of Patients on Hydrocodone Combination Products, Oxycodone Combination Products, Oxycodone ER, Oxycodone IR, January 01, 2010 through December 31, 2011 cumulative**

| | | DECILES | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | Number of sample patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| HYDROCODONE COMBO | 16,281,353 | 2 - 3 | 3 - 4 | 4 - 5 | 5 - 6 | 6 - 8 | 8 - 11 | 11 - 16 | 16 - 32 | 32 - 109 | 109 - 730 |
| OXYCODONE COMBO | 5,497,455 | 2 - 3 | 3 - 4 | 4 - 5 | 5 - 6 | 6 - 6 | 6 - 8 | 8 - 12 | 12 - 23 | 23 - 59 | 59 - 730 |
| OXYCODONE IR | 1,168,258 | 2 - 4 | 4 - 6 | 6 - 8 | 8 - 11 | 11 - 19 | 19 - 31 | 31 - 47 | 47 - 93 | 93 - 221 | 221 - 730 |
| OXYCODONE ER | 70,654 | 2 - 6 | 6 - 10 | 10 - 16 | 16 - 23 | 23 - 31 | 31 - 31 | 31 - 37 | 37 - 62 | 62 - 100 | 100 - 664 |

*Source: Source Healthcare Analytics ProMetis Lx® , January 2010-December 2011, extracted January, 2011, Source File: SHACPA 2009-2039 Hydrocodone Deciles 01-31-12.xls*

**TABLE 5.**

| Diagnoses Associated with Use (by grouped ICD-9 codes) for Selected Opioids as Reported by Office-Based Physicians in the U.S., Jan 2007-Nov 2011 cumulative | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Hydrocodone Combo | | Oxycodone Combo | | Oxycodone IR | | Morphine ER | | Morphine IR | |
| | N(000) | % | N(000) | % | N(000) | % | N(000) | % | N(000) | % |
| **Total Market** | **2,850** | ***100%*** | **1,406** | ***100%*** | **566** | ***100%*** | **2,618** | ***100%*** | **407** | ***100%*** |
| **Diseases of the Musculoskeletal System and Connective Tissue (710-739)** | 699 | *25%* | 287 | *20%* | 230 | *41%* | 1,781 | *68%* | 226 | *56%* |
| **Disease of Respiratory System (462-493)** | 594 | *21%* | 31 | *2%* | | | | | | |
| **Fractures, Sprains, Contusions, Injuries (800-999)** | 547 | *19%* | 368 | *26%* | 43 | *8%* | 89 | *3%* | 15 | *4%* |
| **All others** | 360 | *13%* | 102 | *7%* | 13 | *2%* | 64 | *2%* | 27 | *7%* |
| **Follow up examinations** | 286 | *10%* | 198 | *14%* | 11 | *2%* | 113 | *4%* | 21 | *5%* |
| **Headaches and Nerve Pain (337-359)** | 98 | *3%* | 51 | *4%* | 213 | *38%* | 392 | *15%* | 81 | *20%* |
| **Fever and General Symptoms (780-789)** | 96 | *3%* | 53 | *4%* | 28 | *5%* | 64 | *2%* | 25 | *6%* |
| **Neoplasms (140-239)** | 70 | *2%* | 5 | *0%* | 31 | *5%* | 102 | *4%* | 2 | *0%* |
| **Disease of Genitourinary System (592-626)** | 62 | *2%* | 311 | *22%* | | | 11 | *0%* | 9 | *2%* |
| **Bacterial, Viral and Parasitic Infections (001-138)** | 39 | *1%* | 4 | *0%* | 1 | *0%* | 8 | *0%* | 2 | *0%* |

*Encuity Research LLC. Physician Drug and Diagnosis Audit, Jan07-Nov11. Extracted January 2012, Source Files: PDDA 2009-2039 Hydrocodone, oxycodone, morphine, hydromorphone DX4 (new grouping) 01-20-12.xls; PDDA_2009-2039_Oxycodone_DX4_01-20-12(2).xls; PDDA_2009-2039_Morphine_DX4_01-20-12(1).xls*

## APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

### *IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail*

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### *IMS Vector One®: National (VONA)*

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

### *IMS Vector One®: Total Patient Tracker (TPT)*

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

### *Source Healthcare Analytics' ProMetis Lx®*

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types,

including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

***Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)***

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Encuity Research, LLC., uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned.

# 4 CSS Summary Review

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

**Date:** November 13, 2012

**To:** Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

**Through:** Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

**From:** Lori A. Love, M.D., Ph.D., Medical Officer
James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

**Subject:** NDA 202-880 - Zogenics Inc. (Hydrocodone Extended Release Capsules)
**Indication:** Management of moderate to severe pain requiring a continuous, around-the-clock opioid therapy for an extended period of time.
**Dosages:** 10, 15, 20, 30, 40, and 50 mg Hydrocodone Bitartrate per capsule
**Sponsor:** Zogenics Inc.

**Materials reviewed:** NDA 202,880

## I. Summary

On May 1, 2012, Zogenics Inc. filed New Drug Application (NDA) 202-880 for Zohydro ER (Hydrocodone Bitartrate Extended Release Capsules). On December 7, 2012, a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) will be held to discuss the safety, efficacy, and concerns about the abuse liability associated with Zohydro ER. We provide below background information with our conclusions concerning NDA 202-880.

## II. Background

The NDA for Zohydro ER (Hydrocodone Bitartrate Extended Release Capsules)7 was submitted to the FDA on May 1, 2012. This product is under development for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Zohydro ER, intended for oral administration every 12 hours, will be available at dosage strengths ranging from 10 to 50 mg hydrocodone bitartrate per capsule.

Zohydro ER is a single-entity extended-release formulation that utilizes the Spheroidal Oral Drug Absorption System (SODAS) to control the release of hydrocodone bitartrate.8 The NDA for Zohydro ER was not submitted as an abuse deterrent formulation. Currently, all approved analgesic hydrocodone products are combination products for immediate release. If approved, Zohydro ER would be the first single-entity product containing hydrocodone bitartrate.

As a single-entity product containing hydrocodone, Zohydro ER is a Schedule II narcotic in the Controlled Substances Act (CSA). This differs from the Schedule III status of currently available hydrocodone products all of which are combination products with limited amounts of hydrocodone. This difference is due to the differential scheduling of hydrocodone drug substance versus hydrocodone containing combination products under the CSA. Hydrocodone drug substance is listed in Schedule II of the CSA.9 Products containing hydrocodone (also known as dihydrocodeinone) are in Schedule III if they contain "Not more than 300 milligrams of dihydrocodeinone per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts."10

## III. Conclusions

CSS has the following conclusions regarding Zohydro ER.

1. Zohydro ER, if approved by the FDA, will be the first extended release, single entity product containing hydrocodone bitartrate.

2. Zohydro ER is in Schedule II of the Controlled Substances Act.

3. Zohydro ER is not an abuse deterrent product.

---

7 http://www.zogenix.com/content/pipeline/zohydro.htm
8 http://www.prnewswire.com/news-releases/zogenix-submits-new-drug-application-nda-to-us-food-and-drug-administration-fda-for-zohydro-for-treatment-of-chronic-pain-149799215.html
9 21 U.S.C. 812(c)(Schedule II)((a)(1)
10 21 U.S.C. 812(c)(Schedule III)(d)(4)

4. Published human abuse potential studies indicate that single entity hydrocodone or hydrocodone combination products produce in a dose-dependent manner typical mu-opioid agonist activity similar to morphine, oxycodone and hydromorphone, including subjective effects such as "drug liking' and “high.” Hydrocodone, as single entity and in combination with other drugs, produces subjective abuse-related effects at doses of hydrocodone bitartrate equal to or greater than 15 mg when taken orally (Walsh *et al*., 2008; Zacny and Gutierrez, 2008). When injected intravenously, hydrocodone hydrochloride produces significant abuse-related subjective effects at a 10 mg dose (Stoops *et al*., 2010).

5. If approved and marketed, Zohydro ER will be abused, possibly at a rate greater than that of currently available hydrocodone combination products.

## IV. Discussion

A review of the recent scientific literature of the relative abuse potential of hydrocodone in humans reveals that hydrocodone as a single entity [Schedule II] or in combination products [Schedule III] produces typical mu-opioid agonist activity similar to morphine, oxycodone and hydromorphone [all Schedule II] in a dose-related manner (Zacny 2003, Zacny *et al*, 2005, Zacny and Gutierrez, 2008 and 2009, Walsh *et al*. 2008, Stoops *et al*. 2010). These effects include subjective opioid effects such as "drug liking" and “high.” Depending on the study population and product administered, unpleasant effects such as dizziness and increased rating of nausea also occur.

All studies were crossover, placebo controlled designs, and enrolled non-opioid-dependent subjects. Some of the methodological variables differentiated these studies. These variables included the subject population studied, the various formulations of hydrocodone administered and routes of administration. One of these studies evaluated the abuse potential of hydrocodone single entity when used intravenously (Stoops *et al*. 2010), while the others used oral administration. The number of subjects included in these studies varied from nine to twenty. Some of the studies included subjects with prior history of recreational drug use, whereas others enrolled subjects with a prior history of opioid abuse or prescription opioid abuse. In all the studies, the reinforcing effects of several doses of either compounded single entity hydrocodone products, or hydrocodone combined with either acetaminophen or homatropine, were compared to the effects mediated by other prescription opioids. The single entity products, as well as the high strength hydrocodone combination products studied are not currently approved marketed products in the United States.

These studies showed that hydrocodone, as single entity and in combination with other drugs, produces subjective abuse-related effects at doses of hydrocodone bitartrate equal to or greater than 15 mg when taken orally. When administered intravenously, a dose of 10 mg of hydrocodone hydrochloride was associated with significantly higher levels of “drug liking” compared to placebo (Stoops *et al*. 2010). Although the preferred

route of abuse of marketed hydrocodone combination products is oral followed by lower levels of intranasal abuse, the intranasal and intravenous routes of administration might become more relevant routes of administration for the single entity product. (Butler *et al*. 2011)

It is relevant to mention that human abuse potential studies measure the relative abuse potential of a drug when compared to another drug of abuse, and contribute to the assessment of the likelihood of abuse of a drug when introduced on the market. However, these studies do not measure several variables that might impact the abuse of a product when introduced to the market. These abuse potential studies do not measure intrinsic properties of a formulation or other factors that might impact the levels of abuse of a particular formulation, such as availability of other opioid products, information available on the abuse of the novel product, street prices, and fads among other factors.

As a hydrocodone single-entity, extended-release product, it is expected that Zohydro ER (if approved and marketed) will be associated with higher levels of abuse than the hydrocodone combination products. These expected higher levels of abuse are based on what has been observed for oxycodone products. Like hydrocodone, oxycodone is also marketed as a combination product, but there are also single-entity, extended release (ER) products available. As a result, the available data on drug abuse of oxycodone combination and single-entity ER products can provide indirect evidence for the abuse patterns we might see with Zohydro ER.

The 2008 national estimates of abuse-related Emergency Department (ED) visits were obtained from the Drug Abuse Warning Network (DAWN). To adjust for drug utilization, the Total Number of Tablets Dispensed was obtained from IMS Health and used as the denominator to compute abuse ratios11. The abuse ratio for hydrocodone combination products was 14 ED visits per million tablets dispensed. The abuse ratio for oxycodone combination products was 24 ED visits per million tablets dispensed, compared to 85 ED visits per million tablets dispensed for oxycodone single-entity ER products. This difference is substantial and it is likely that similar patterns will be observed between hydrocodone combination products and Zohydro ER.

## V. References

Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH, 2011, Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduction Journal, 8:29

11 Levels of abuse were measured using “abuse ratios.” “Abuse ratios” measure the occurrence of an abuse related event, such as an ED visit (numerator) per amount of drug available for abuse (denominator), relative to other drugs with similar pharmacology and medical use (comparator products).

Stoops, WW, Hatton, KW, Lofwall, MR, Nuzzo, PA, Walsh, SL, 2010, Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies, Psychopharmacology 212:193-203.

Walsh, SL, Nuzzo, PA, Lofwall, MR, Holtman Jr, JR, 2008, The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abuses, Drug Alcohol Depend, 98:191-202.

Zacny JP, Gutierrez, S., 2009, Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers, Drug Alcohol Depend, 101:107-114.

Zacny, JP, 2003, Characterizing the subjective, psychomotor, and physiological effects of hydrocodone combination product (Hycodan) in non-drug-abusing volunteers, Psychopharmacology, 165:146-156.

Zacny, JP, Gutierrez, S, 2008, Subjective, psychomotor, and physiological effects profile of hydrocodone/acetaminophen and oxycodone/acetaminophen combination products, Pain Med, 9(4):433-443.

Zacny, JP, Gutierrez, S, Bolbolan, SA, 2005, Profiling the subjective, psychomotor, and physiological effects of hydrocodone/acetaminophen product in recreational drug users, Drug Alcohol Depend, 78, 243-252.

# 5 Topics for Advisory Committee Discussion

1. **Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?**

2. **Has the applicant demonstrated that Zohydro ER is safe in the intended population?**

3. **Do any of the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids?**

4. **Are there data that support the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS?**

5. **Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?**